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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GLAWE, DELFS, MOLL & PARTNER
Rothenbaumchausse 58
20148 Hamburg
ALLEMAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	20.03.2001
Applicant's or agent's file reference UNIXO31PEP	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/27401	18/11/1999	18/11/1998

Applicant
UNIVERSITY OF FLORIDA et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Longo, E Tel.+49 89 2399-8141

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
UNIXO31PEP		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/27401	18/11/1999	18/11/1998
International Patent Classification (IPC) or national classification and IPC		
A61K9/00		
Applicant		
UNIVERSITY OF FLORIDA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/06/2000	20.03.2001
Name and mailing address of the international preliminary xamining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rauter, A Telephone No. +49 89 2399 8645

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/27401

I. **Basis of the report**

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-53 as originally filed

Claims, No.:

1-27 as received on 19/02/2001 with letter of 16/02/2001

Drawings, sheets:

1/10-10/10 as originally filed

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ th claims, Nos.:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/27401

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. R asoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1 - 27
	No:	Claims
Inventive step (IS)	Yes:	Claims 1 - 27
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1 - 27
	No:	Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

Int mational application No. PCT/US99/27401

SECTION V. .....

1. Reference is made to the following documents:

   D1: WO-A-9 853 767
   D2: WO-A-9 947 726

2. The present application satisfies the criteria set forth in Article 33(1)-(4) PCT because the subject-matter of claims 1 - 27 is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT), involves an inventive step (Rule 65(1)(2) PCT) and is considered industrially applicable.

   D1 is concerned with a method of producing a film coating by matrix assisted pulsed laser deposition on large sensor parts. D2 discloses a method for coating a plurality of host particles with coating particles by vapour deposition, preferably laser ablation. In the latter document, TiO_2 or Ag targets to produce coatings on particles, such as SiO_2 are mentioned, however the said coatings are not biodegradable or biocompatible and there is no disclosure or suggestion that such coatings could be used for medicinal applications. There is no disclosure available which could have rendered presently claimed subject-matter obvious, in particular that medicaments (see present claim 1) could be provided which show the derived controlled drug delivery.

   The formulation of claim 11, the kit of claim 22, the use of claim 24, the method of claim 25 as well as all the dependent claims comprise the new and inventive product, ie the medicament according to claim 1, and thus are considered to fulfill the requirements of Article 33(1)-(3) PCT. There exists no doubt that the claimed subject-matter is industrially applicable as required by Article 33(4) PCT.

SECTION VII. .....

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

2. The description is not in conformity with the claims.

SECTION VIII. .....

1. The term "about" used in the dependent claim 14 renders the defined range of the said claim vague and unclear (Article 6 PCT).

2. According to claim 2 the coating particles can be selected inter alia from cellulose "compounds", however, it appears that only "cellulose" has been originally disclosed, thus Article 34(2)(b) PCT is infringed.

Claims

1. A medicament comprising a plurality of coated drug particles, each having an average particle size of less than 500 μm in diameter, the surface of said particles comprising at least a first layer of biodegradable and biocompatible polymeric coating particles, wherein the average thickness of said coating layer is between 1 and 500 nm, the coated drug particles being obtainable through a process comprising depositing said polymeric coating particles onto the surface of host drug particles by a process comprising pulsed laser ablation.

2. The medicament according to claim 1, wherein said coating particles are selected from the group consisting of PLA, PGA, PLGA and cellulose compounds.

3. The medicament according to claim 1 or 2, wherein said drug particles have an average particle size of less than 400 μm in diamter, preferably less than 300 μm, further preferred less than 200 μm, further preferred less than 100 μm, further preferred less than 50 μm, further preferred less than 10 μm, further preferred less than 5 μm, further preferred less than 1 μm, further preferred less than 0.1 μm.

4. The medicament according to any preceding claim, wherein the average thickness of said coating layer is between 1 and 400 nm, preferably 2 and 300 nm, further preferred 3

and 200 nm, further preferred 4 and 100 nm, further preferred 5 and 50 nm.

5. The medicament according to any of the claims 1 to 3, wherein the average thickness of said coating layer is between 50 and 500 nm, preferably 100 and 500 nm, further preferred 150 and 500 nm, further preferred 200 and 500 nm, further preferred 300 and 500 nm.

6. The medicament according to any preceding claim, wherein the average size of the polymeric coating particles is less than 50 nm in diameter, preferably less than 40 nm, more preferred less than 30 nm, more preferred less then 20 nm, more preferred less than 10 nm, more preferred less than 5 nm.

7. The medicament according to any preceding claim, wherein said polymeric coating particles are applied to the surface of said drug particles to form a continuous layer.

8. The medicament according to any preceding claim, wherein said polymeric coating particles are applied to the surface of said drug particles to form a discontinuous layer.

9. The medicament according to any preceding claim, wherein said coated drug particles comprise an anti-allergic, an antibiotic, an anti-inflammatory, or a bronchodilatory drug.

10. The medicament according to any preceding claim, wherein said drug particles are selected from the group consist-

- ing of budesonide, triamcinolone acetonide, and rifampicin.

11. A pharmaceutical formulation comprising the medicament of any preceding claim.

12. The formulation according to claim 11, comprising from 0.01 % to 10 % by weight of said medicament relative to the total weight of the formulation.

13. The formulation according to claim 11 or 12, containing from 0.1 % to 1 % by weight of said medicament relative to the total weight of the formulation.

14. The formulation according to any one of claims 11 to 13, comprising a respirable fraction of from about 20 % to about 50 % or more by weight of said medicament.

15. The formulation according to any of claims 11 to 13, further comprising a second medicament.

16. The formulation according to claim 15, wherein said second medicament is a particulate medicament.

17. The formulation according to claim 15, wherein said second medicament comprises a medicament in accordance with any one of claims 1 to 10.

18. The formulation according to any one of claims 11 to 17, comprising a first bronchodilatory medicament and a second medicament selected from the group consisting of an anti-inflammatory agent, a bronchodilatory agent, an an-

tibiotic agent, and an anti-allergic agent.

19. The formulation according to any one of claims 11 to 18, further comprising a vehicle suitable for aerosol administration of said formulation.

20. The formulation according to claim 19 further comprising a propellant.

21. The formulation according to claim 20, wherein said propellant is selected from the group consisting of a fluorocarbon and a hydrogen-containing chlorofluorocarbon.

22. A therapeutic kit comprising the medicament of any one of claims 1 to 10, or the formulation according to any one of claims 11 to 21, and instructions for the administration of said medicament.

23. The therapeutic kit of claim 22, further comprising an aerosol delivery apparatus or a medical device suitable for pulmonary administration of said medicament.

24. The use of coated drug particles as defined in any of the claims 1 to 10 or of a formulation according to any of the claims 11 to 21 for the manufacture of a medicament for treating a respiratory disorder or a pulmonary infection in a human patient.

25. A method of preparing coated drug particles as defined in any of the claims 1 to 10, the method comprising depositing onto the surface of a host drug particle at least a

first layer that comprises a plurality of polymeric coating particles by a process comprising pulsed las r ablation under vacuum.

26. The method according to claim 25, wherein said pulsed laser ablation comprises a laser having a wavelength of about 240 to about 280 nm.

27. The method according to claim 25 or 26, wherein said pulsed laser ablation comprises a laser having a wavelength of about 248 nm.

Amended claims